

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising:
a drug retained in a solid matrix in a manner causing release of said drug from said solid matrix when said solid matrix is in the stomach, said solid matrix when in the stomach being of a size large enough to promote retention of said solid matrix in the stomach during the fed mode, and

a fed mode inducing agent selected from the group consisting of:

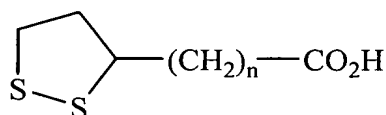
(a) glycine, glycyglycine and salts thereof,

(b) C₄-C₈ sugar alcohols,

(c) alkali and alkaline earth metal docusates,

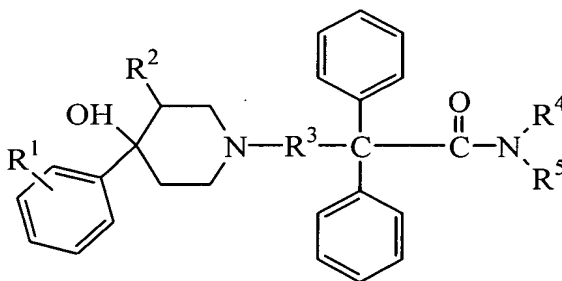
(d) β-casomorphins,

(e) dithioorganic acids of the formula



in which n is 3 to 13,

(f) 2,2-diaryl-4-(4'-aryl-4'-hydroxypiperidino)butyramides of the formula



in which:

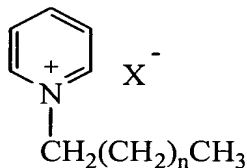
R¹ is a member selected from the group consisting of H, lower alkyl, and halo,

R² is a member selected from the group consisting of H and methyl,

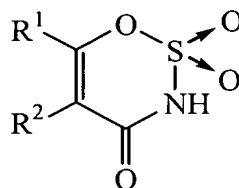
R³ is a member selected from the group consisting of —CH₂CH₂— and —CH(CH₃)CH₂—,

R⁴ is lower alkyl, and

- 26 R^5 is lower alkyl,
 27 (g) arginine and arginine salts,
 28 (h) the dipeptide Trp-Trp and salts thereof,
 29 (i) alkyl pyridinium halides of the formula



- 30
 31 in which n is 8 to 20 and X is halide,
 32 (j) dihydroxybenzoic acids, *claim 44 G6751C Ac17*
 33 (k) stevioside,
 34 (l) alkyl esters of N-L- α -aspartyl L-phenylalanine,
 35 (m) aspartic acid and salts thereof, and
 36 (n) 3,4-dihydro-1,2,3-oxathiazin-4-ones of the formula



- 37
 38 in which R^1 and R^2 are independently selected from the
 39 group consisting of H and C_1 - C_{10} alkyl, and salts thereof
 40 in an amount that causes onset of the fed mode.

Sub A.
 1 **2.** A pharmaceutical composition in accordance with claim 1 in which
 2 said fed mode inducing agent is retained in said solid matrix with said drug, said solid
 3 matrix causing release of both said fed mode reducing agent and said drug in a sustained
 4 manner. *42, "inducing" intend?*

1 **3.** A pharmaceutical composition in accordance with claim 1 in which
 2 said fed mode inducing agent resides in a surface coating or layer on said solid matrix,
 3 said surface coating or layer permitting substantially immediate release of said fed mode
 4 reducing agent upon contact with gastric fluid while said solid matrix causes release of
 5 said drug in a sustained manner.

4. A pharmaceutical composition in accordance with claim 1 in which said fed mode inducing agent is separate from said solid matrix, said solid matrix causing release of drug in a sustained manner.

5. A pharmaceutical composition in accordance with claim 1 in which the size of said solid matrix prior to ingestion is sufficiently large to promote retention of said solid matrix in the stomach during the fed mode.

6. A pharmaceutical composition in accordance with claim 1 in which said solid matrix swells or expands upon contact with gastric fluid to a size sufficiently large to promote retention of said solid matrix in the stomach during the fed mode.

7. A pharmaceutical composition in accordance with claim 1 in which said fed mode inducing agent is a member selected from the group consisting of glycine, glycylglycine, and salts thereof.

8. A pharmaceutical composition in accordance with claim 7 in which the amount of said fed mode inducing agent is from about 1 mg to about 500 mg.

9. A pharmaceutical composition in accordance with claim 7 in which the amount of said fed mode inducing agent is from about 5 mg to about 150 mg.

10. A pharmaceutical composition in accordance with claim 1 in which said fed mode inducing agent is a C₄-C₈ sugar alcohol.

11. A pharmaceutical composition in accordance with claim 10 in which said C₄-C₈ sugar alcohol is xylitol.

12. A pharmaceutical composition in accordance with claim 10 in which the amount of said C₄-C₈ sugar alcohol is from about 30 mg to about 1000 mg.

13. A pharmaceutical composition in accordance with claim 10 in which the amount of said C₄-C₈ sugar alcohol is from about 100 mg to about 800 mg.

14. A pharmaceutical composition in accordance with claim 1 in which said fed mode inducing agent is a member selected from the group consisting of alkali and alkaline earth metal docusates.

1 **15.** A pharmaceutical composition in accordance with claim **14** in
2 which said fed mode inducing agent is a member selected from the group consisting of
3 calcium docusate and sodium docusate.

1 **16.** A pharmaceutical composition in accordance with claim **14** in
2 which said fed mode inducing agent is sodium docusate.

1 **17.** A pharmaceutical composition in accordance with claim **14** in
2 which the amount of said fed mode inducing agent is from about 30 mg to about
3 1000 mg.

1 **18.** A pharmaceutical composition in accordance with claim **14** in
2 which the amount of said fed mode inducing agent is from about 50 mg to about 400 mg.

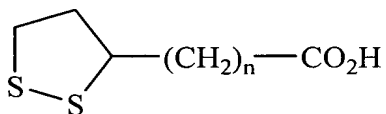
1 **19.** A pharmaceutical composition in accordance with claim **1** in which
2 said fed mode inducing agent is a β -casomorphin.

1 **20.** A pharmaceutical composition in accordance with claim **19** in
2 which said β -casomorphin is bovine β -casomorphin.

1 **21.** A pharmaceutical composition in accordance with claim **19** in
2 which the amount of said β -casomorphin is from about 1 mg to about 300 mg.

1 **22.** A pharmaceutical composition in accordance with claim **19** in
2 which the amount of said β -casomorphin is from about 5 mg to about 150 mg.

1 **23.** A pharmaceutical composition in accordance with claim **1** in which
2 said fed mode inducing agent is a dithioorganic acid of the formula



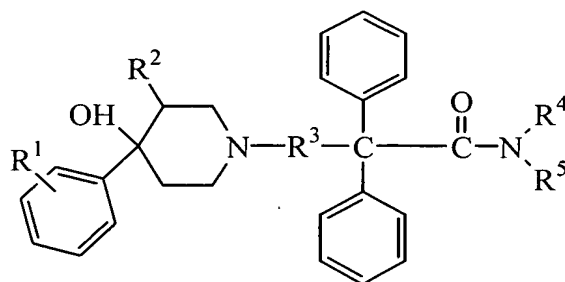
3
4 in which n is 3 to 13.

1 **24.** A pharmaceutical composition in accordance with claim **23** in
2 which said dithioorganic acid is α -lipoic acid.

1 **25.** A pharmaceutical composition in accordance with claim **23** in
2 which the amount of said dithioorganic acid is from about 30 mg to about 1000 mg.

1 ~~26.~~ A pharmaceutical composition in accordance with claim ~~23~~ in
2 which the amount of said dithioorganic acid is from about 40 mg to about 300 mg.

1 ~~27.~~ A pharmaceutical composition in accordance with claim ~~1~~ in which
2 said fed mode inducing agent is a 2,2-diaryl-4-(4'-aryl-4'-hydroxypiperidino)butyramide
3 of the formula



4
5 in which:

6 R¹ is a member selected from the group consisting of H, lower alkyl, and
7 halo,

8 R² is a member selected from the group consisting of H and methyl,

9 R³ is a member selected from the group consisting of —CH₂CH₂— and
10 —CH(CH₃)CH₂—,

11 R⁴ is lower alkyl, and

12 R⁵ is lower alkyl.

1 ~~28.~~ A pharmaceutical composition in accordance with claim ~~27~~ in
2 which:

3 R¹ is a member selected from the group consisting of H, C₁-C₃ alkyl,
4 fluoro, and chloro,

5 R² is a member selected from the group consisting of H and methyl,

6 R³ is a member selected from the group consisting of —CH₂CH₂— and
7 —CH(CH₃)CH₂—,

8 R⁴ is C₁-C₃ alkyl, and

9 R⁵ is C₁-C₃ alkyl.

1 ~~29.~~ A pharmaceutical composition in accordance with claim ~~27~~ in
2 which R¹ is 4-chloro, R² is H, R³ is —CH₂CH₂—, R⁴ is CH₃, and R⁵ is CH₃.

1 ~~30.~~ A pharmaceutical composition in accordance with claim 27 in
2 which the amount of said 2,2-diaryl-4-(4'-aryl-4'-hydroxypiperidino)butyramide is from
3 about 0.5 mg to about 300 mg.

1 ~~31.~~ A pharmaceutical composition in accordance with claim 27 in
2 which the amount of said 2,2-diaryl-4-(4'-aryl-4'-hydroxypiperidino)butyramide is from
3 about 2 mg to about 15 mg.

1 ~~32.~~ A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is a member selected from the group consisting of arginine
3 and arginine salts.

1 ~~33.~~ A pharmaceutical composition in accordance with claim 32 in
2 which the amount of said fed mode inducing agent is from about 3 mg to about 300 mg.

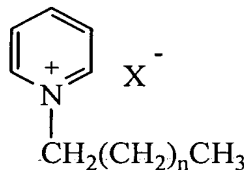
1 ~~34.~~ A pharmaceutical composition in accordance with claim 32 in
2 which the amount of said fed mode inducing agent is from about 30 mg to about 150 mg.

1 ~~35.~~ A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is a member selected from the group consisting of the
3 dipeptide Trp-Trp and Trp-Trp salts.

1 ~~36.~~ A pharmaceutical composition in accordance with claim 35 in
2 which the amount of said Trp-Trp is from about 0.05 mg to about 300 mg.

1 ~~37.~~ A pharmaceutical composition in accordance with claim 35 in
2 which the amount of said Trp-Trp is from about 0.5 mg to about 10 mg.

1 ~~38.~~ A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is an alkyl pyridinium halide of the formula



3
4 in which n is 10 to 20 and X is halide.

1 39. A pharmaceutical composition in accordance with claim 38 in
2 which n is 12 to 16 and X is chloride.

1 40. A pharmaceutical composition in accordance with claim 38 in
2 which said alkyl pyridinium halide is cetyl pyridinium chloride.

1 41. A pharmaceutical composition in accordance with claim 38 in
2 which the amount of said alkyl pyridinium halide is from about 0.1 mg to about 200 mg.

1 42. A pharmaceutical composition in accordance with claim 38 in
2 which the amount of said alkyl pyridinium halide is from about 0.5 mg to about 50 mg.

1 43. A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is a dihydroxybenzoic acid.

1 44. A pharmaceutical composition in accordance with claim 43 in
2 which said dihydroxybenzoic acid is gentisic acid.

1 45. A pharmaceutical composition in accordance with claim 43 in
2 which the amount of said dihydroxybenzoic acid is from about 3 mg to about 300 mg.

1 46. A pharmaceutical composition in accordance with claim 43 in
2 which the amount of said dihydroxybenzoic acid is from about 10 mg to about 100 mg.

1 47. A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is retained in said dosage form in such a manner that said
3 fed mode inducing agent is released substantially immediately into gastric fluid upon
4 contact of said dosage form with said gastric fluid while said drug is released into said
5 gastric fluid in a sustained manner by dissolution and diffusion of said drug out of said
6 solid matrix, by erosion or dissolution of said matrix, or by osmotic pressure within said
7 solid matrix.

1 48. A pharmaceutical composition in accordance with claim 1 in which
2 said fed mode inducing agent is retained in said dosage form in such a manner that both
3 said drug and said fed mode inducing agent are released into gastric fluid in a sustained
4 manner by dissolution and diffusion of said drug and said fed mode inducing agent out of

5 said solid matrix, by erosion or dissolution of said matrix, or by osmotic pressure within
6 said solid matrix.

1 (49.) A pharmaceutical composition in accordance with claim 1 in which
2 said solid matrix is a member selected from the group consisting of cellulose polymers
3 and polyethylene oxide.

1 (50.) A pharmaceutical composition in accordance with claim 49 in
2 which said solid matrix is a member selected from the group consisting of
3 hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose,
4 hydroxypropylmethylcellulose, carboxymethylcellulose, and polyethylene oxide.

1 (51.) A pharmaceutical composition in accordance with claim 50 in
2 which said solid matrix is a member selected from the group consisting of
3 hydroxyethylcellulose, hydroxypropylcellulose, and polyethylene oxide.

1 498 480
2 52. A pharmaceutical composition in accordance with claim 1 in which
3 said fed mode inducing agent is contained in a solid coating adhering to a surface of said
solid matrix.

1 53. A pharmaceutical composition in accordance with claim 52 in
2 which said solid coating is comprised of said fed mode inducing agent suspended in a
3 water-soluble matrix.

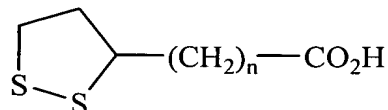
1 54. A pharmaceutical composition in accordance with claim 52 in
2 which said water-soluble matrix is a member selected from the group consisting of
3 celluloses, vinyls, glycols and carbohydrates.

1 55. A pharmaceutical composition in accordance with claim 52 in
2 which said water-soluble matrix is a member selected from the group consisting of
3 sodium carboxymethylcellulose, sodium starch glycolate, crospovidone, microcrystalline
4 cellulose, lactose, and substituted hydroxypropylcellulose.

1 56. A method for pharmacologically inducing the fed mode in a
2 subject, said method comprising administering to said subject a fed mode inducing agent
3 selected from the group consisting of:

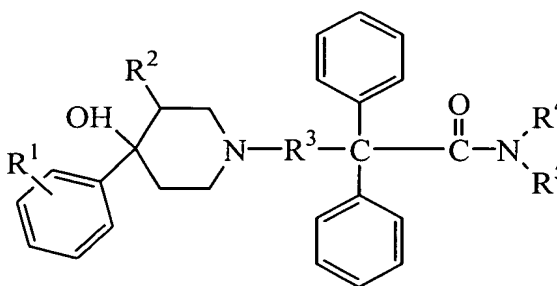
4 (a) glycine, glycylglycine and salts thereof,

- (b) C₄-C₈ sugar alcohols,
 (c) alkali and alkaline earth metal docusates,
 (d) β-casomorphins,
 (e) dithioorganic acids of the formula



in which n is 3 to 13,

- (f) 2,2-diaryl-4-(4'-aryl-4'-hydroxypiperidino)butyramides of the formula



in which:

R¹ is a member selected from the group consisting of H,
 lower alkyl, and halo,

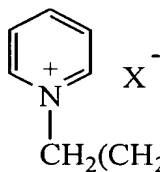
R² is a member selected from the group consisting of H and
 methyl,

R³ is a member selected from the group consisting of —
 CH₂CH₂— and —CH(CH₃)CH₂—,

R⁴ is lower alkyl, and

R⁵ is lower alkyl,

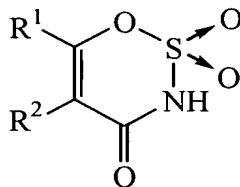
- (g) arginine and arginine salts,
 (h) the dipeptide Trp-Trp and salts thereof,
 (i) alkyl pyridinium halides of the formula



in which n is 10 to 20 and X is halide,

- (j) dihydroxybenzoic acids,

- 29 (k) stevioside,
30 (l) alkyl esters of N-L- α -aspartyl L-phenylalanine,
31 (m) aspartic acid and salts thereof, and
32 (n) 3,4-dihydro-1,2,3-oxathiazin-4-ones of the formula



- 33
34 in which R¹ and R² are independently selected from the group
35 consisting of H and C₁-C₁₀ alkyl, and salts thereof,
36 in an amount that causes onset of the fed mode.

1 **57.** A method in accordance with claim **56** in which said fed mode
2 inducing agent is a member selected from the group consisting of glycine, glycylglycine,
3 and salts thereof.

1 **58.** A method in accordance with claim **57** in which the amount of said
2 fed mode inducing agent is from about 1 mg to about 500 mg.

1 **59.** A method in accordance with claim **57** in which the amount of said
2 fed mode inducing agent is from about 5 mg to about 150 mg.

1 **60.** A method in accordance with claim **56** in which said fed mode
2 inducing agent is a C₄-C₈ sugar alcohol.

1 **61.** A method in accordance with claim **60** in which said C₄-C₈ sugar
2 alcohol is xylitol.

1 **62.** A method in accordance with claim **60** in which the amount of said
2 C₄-C₈ sugar alcohol is from about 30 mg to about 1000 mg.

1 **63.** A method in accordance with claim **60** in which the amount of said
2 C₄-C₈ sugar alcohol is from about 100 mg to about 800 mg.

1 **64.** A method in accordance with claim **56** in which said fed mode
2 inducing agent is a member selected from the group consisting of alkali and alkaline earth
3 metal docusates.

1 **65.** A method in accordance with claim **64** in which said fed mode
2 inducing agent is a member selected from the group consisting of calcium docusate and
3 sodium docusate.

1 **66.** A method in accordance with claim **64** in which said fed mode
2 inducing agent is sodium docusate.

1 **67.** A method in accordance with claim **64** in which the amount of said
2 fed mode inducing agent is from about 30 mg to about 1000 mg.

1 **68.** A method in accordance with claim **64** in which the amount of said
2 fed mode inducing agent is from about 60 mg to about 400 mg.

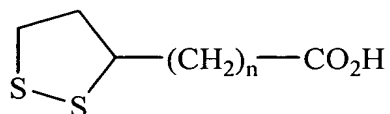
1 **69.** A method in accordance with claim **56** in which said fed mode
2 inducing agent is a β -casomorphin.

1 **70.** A method in accordance with claim **69** in which said
2 β -casomorphin is bovine β -casomorphin.

1 **71.** A method in accordance with claim **69** in which the amount of said
2 β -casomorphin is from about 1 mg to about 300 mg.

1 **72.** A method in accordance with claim **69** in which the amount of said
2 β -casomorphin is from about 5 mg to about 150 mg.

1 **73.** A method in accordance with claim **56** in which said fed mode
2 inducing agent is a dithioorganic acid of the formula

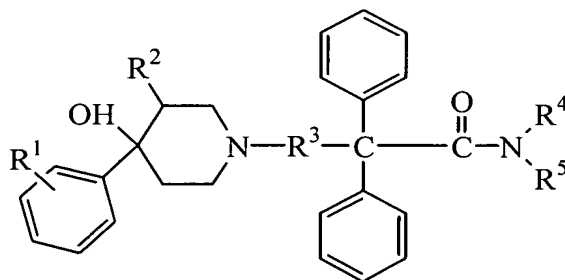


1 **74.** A method in accordance with claim **73** in which said dithioorganic
2 acid is α -lipoic acid.

1 **75.** A method in accordance with claim **73** in which the amount of said
2 dithioorganic acid is from about 30 mg to about 1000 mg.

1 76. A method in accordance with claim ~~73~~ in which the amount of said
2 dithioorganic acid is from about 40 mg to about 300 mg.

1 77. A method in accordance with claim ~~56~~ in which said fed mode
2 inducing agent is a 2,2-diaryl-4-(4'-aryl-4'-hydroxypiperidino)butyramide of the formula



3
4 in which:

5 R¹ is a member selected from the group consisting of H, lower alkyl, and
6 halo,

7 R² is a member selected from the group consisting of H and methyl,

8 R³ is a member selected from the group consisting of —CH₂CH₂— and
9 —CH(CH₃)CH₂—,

10 R⁴ is lower alkyl, and

11 R⁵ is lower alkyl.

1 78. A method in accordance with claim ~~77~~ in which:

2 R¹ is a member selected from the group consisting of H, C₁-C₃ alkyl,
3 fluoro, and chloro,

4 R² is a member selected from the group consisting of H and methyl,

5 R³ is a member selected from the group consisting of —CH₂CH₂— and
6 —CH(CH₃)CH₂—,

7 R⁴ is C₁-C₃ alkyl, and

8 R⁵ is C₁-C₃ alkyl.

1 79. A method in accordance with claim ~~77~~ in which R¹ is 4-chloro, R²
2 is H, R³ is —CH₂CH₂—, R⁴ is CH₃, and R⁵ is CH₃.

1 80. A method in accordance with claim ~~77~~ in which the amount of said
2 2,2-diaryl-4-(4'-aryl-4'-hydroxypiperidino)butyramide is from about 0.5 mg to about
3 300 mg.

1 **81.** A method in accordance with claim **77** in which the amount of said
2 2,2-diaryl-4-(4'-aryl-4'-hydroxypiperidino)butyramide is from about 2 mg to about 15 mg.

1 **82.** A method in accordance with claim **56** in which said fed mode
2 inducing agent is a member selected from the group consisting of arginine and arginine
3 salts.

1 **83.** A method in accordance with claim **82** in which the amount of said
2 fed mode inducing agent is from about 3 mg to about 300 mg.

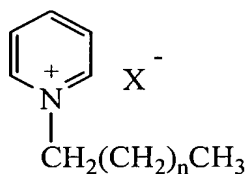
1 **84.** A method in accordance with claim **82** in which the amount of said
2 fed mode inducing agent is from about 30 mg to about 150 mg.

1 **85.** A method in accordance with claim **56** in which said fed mode
2 inducing agent is a member selected from the group consisting of the dipeptide Trp-Trp
3 and Trp-Trp salts.

1 **86.** An oral drug dosage form in accordance with claim **85** in which the
2 amount of said Trp-Trp is from about 0.05 mg to about 300 mg.

1 **87.** An oral drug dosage form in accordance with claim **85** in which the
2 amount of said Trp-Trp is from about 0.5 mg to about 10 mg.

1 **88.** A method in accordance with claim **56** in which said fed mode
2 inducing agent is an alkyl pyridinium halide of the formula



3
4 in which n is 10 to 20 and X is halide.

1 **89.** A method in accordance with claim **88** in which n is 12 to 16 and X
2 is chloride.

1 **90.** A method in accordance with claim **88** in which said alkyl
2 pyridinium halide is cetyl pyridinium chloride.

1 91. A method in accordance with claim 88 in which the amount of said
2 alkyl pyridinium halide is from about 0.1 mg to about 200 mg.

1 92. A method in accordance with claim 88 in which the amount of said
2 alkyl pyridinium halide is from about 0.5 mg to about 50 mg.

1 93. A method in accordance with claim 56 in which said fed mode
2 inducing agent is a dihydroxybenzoic acid.

1 94. A method in accordance with claim 93 in which said
2 dihydroxybenzoic acid is gentisic acid.

1 95. A method in accordance with claim 93 in which the amount of said
2 dihydroxybenzoic acid is from about 3 mg to about 300 mg.

1 96. A method in accordance with claim 93 in which the amount of said
2 dihydroxybenzoic acid is from about 10 mg to about 100 mg.

1 97. A pharmaceutical composition comprising:

2 a drug retained in a first solid matrix in a manner causing release of said
3 drug from first said solid matrix when said first solid matrix is in
4 the stomach, said solid first matrix when in the stomach being of a
5 size large enough to promote the retention of said first solid matrix
6 in the stomach during the fed mode, and

7 a pharmacological fed mode inducing agent active in inducing onset of the
8 fed mode, said fed mode inducing agent retained in a second solid
9 matrix configured to release said fed mode inducing agent into the
10 stomach in a sustained manner.

1 98. A pharmaceutical composition in accordance with claim 97 in
2 which said first solid matrix and said second solid matrix are a common single matrix.

1 99. A pharmaceutical composition in accordance with claim 97 in
2 which said fed mode inducing agent is sufficiently potent that onset of said fed mode
3 results from release of an amount of said fed mode inducing agent that is less than
4 500 mg.